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Original Article

Clinical features and survival outcome of locally advanced extrahepatic cholangiocarcinoma

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Backgrounds/Aims: Little is known about clinical features and survival outcome in locally advanced unresectable extrahepatic cholangiocarcinoma (EHC). The aim was to investigate the clinical features and the survival outcome in these patients, and to evaluate the role of palliative resections in locally advanced unresectable EHC. **Methods:** Between 1995 and 2007, 280 patients with locally advanced unresectable EHC were identified. Clinical, pathologic, and survival data were investigated. A comparative analysis was done between those who received palliative resection (PR) and those who were not operated on (NR). **Results:** The overall median survival of the study population was 10±1 months, and the 3- and 5-year survival rates (YSR) were 8.5% and 2.5%, respectively. The median survival, 3- and 5-YSR of PR were 23 months, 32.1% and 13.1%, respectively. For NR, they were 9 months, 3.9% and 0%, which were significantly worse than PR ($p<0.001$). In univariate analysis, T classification, N classification, tumor location, palliative resection, adjuvant treatment, chemotherapy, and radiation therapy were factors that showed survival difference between PR and NR. Regional lymph node metastasis (RR, 2.084; 95% CI, 1.491-2.914; $p<0.001$), non-resections (RR, 2.270; 95% CI, 1.497-3.443; $p<0.001$), and no chemotherapy (RR, 1.604; 95% CI, 1.095-2.349; $p=0.015$) were identified as risk factors for poor outcome on multivariate analysis. **Conclusions:** Without evidence of systemic disease, palliative resection may provide some survival benefit in selected locally advanced unresectable EHCs and adjuvant treatment may further improve survival outcome. **(Korean J Hepatobiliary Pancreat Surg 2014;18:1-8)**

Key Words: Extrahepatic; Cholangiocarcinoma; Palliative surgery; Survival; Adjuvant therapy

INTRODUCTION

Cholangiocarcinoma can occur anywhere along the biliary tree. Cholangiocarcinoma can be broadly divided into intrahepatic and extrahepatic cholangiocarcinoma. Extrahepatic cholangiocarcinoma can further be divided into perihilar cholangiocarcinoma and distal bile duct cancer.[1] Perihilar cholangiocarcinoma and distal bile duct cancer comprise extrahepatic cholangiocarcinoma (EHC). EHCs are rare malignant tumors in western countries, but they are relatively frequent tumors in some Asian countries.[2,3]

Surgical resection with negative resection margin is the only effective treatment for long-term survival. The 5-year survival rate is reported to range from 30% to 45% after R0 resection, and 14% to 30% after R1 resection.[4-6] Recent advancements of imaging modalities and operative techniques have improved the resection rate of EHCs.[6-8] Yet, less than 30% of EHC patients are known to qualify for formal curative resection and those who are unresectable will receive biliary drainage.[9,10] In addition, even among those who undergo resection with curative intent, only R2 resection will be possible due to severely advanced state. However, not much is known about unresectable EHCs and the benefit of R2 resections in these patients.

The purpose of this study was to investigate the clinical features and the survival outcome of locally advanced unresectable EHCs. Furthermore, the effects of R2 resection in locally advanced unresectable EHCs were examined by comparing the outcomes of those who received R2 resections and those who did not. After fulfilling these aims, preliminary management guidelines for locally advanced unresectable EHCs were constructed.

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METHODS

Between 1995 and 2007, a total of 905 patients were diagnosed as EHC at Seoul National University Hospital. To exclude patients with systemic diseases, 163 patients with evidence of metastasis either on radiologic or operative findings were excluded. Among the remaining 742 patients, 339 patients with R0 resections (45.7%) and 123 patients with R1 resection (16.6%) were also excluded. 280 patients who were identified as inoperable patients due to locally advanced state were included in the analysis. Among them, 39 patients (13.9%) received R2 resections and 241 patients (86.1%) received percutaneous or endoscopic biliary drainage without operation. The former were identified as the palliative resection (PR) group and the latter as the non-resection (NR) group. The patient selection process is described in Fig. 1. Thirty-nine R2 resections included 4 cases of right hemihepatectomy with hepaticojejunostomy, 4 cases of left hemihepatectomy with hepaticojejunostomy, and 31 cases of bile duct segmental resection with hepaticojejunostomy.

Clinical, pathologic, and survival data were evaluated. The clinical data included data on age, sex, tumor location, tumor markers, bilirubin level, drainage method, and adjuvant therapy. T and N classifications were evaluated as pathologic data. For NR group, tentative T and N statuses were classified based on preoperative computed tomography, magnetic resonance imaging, and other preoperative imaging work-up studies. The survival data was obtained and confirmed by the Ministry of Public Administration and Security, Korea.

A comparative analysis on the locally advanced non-resectable EHC patients was done. Student T-tests were done for continuous variables, and chi-squared, Fisher's exact, or likelihood ratio was used for categorical variables where appropriate. For survival analysis, Kaplan-Meier methods and log-rank test was used. Multivariate analysis was done using the Cox regression model. All statistical evaluations were performed using IBM SPSS Statistics 19.0 (IBM, Somers, NY, USA). P-values of less than 0.05 were considered statistically significant.

RESULTS

Overall demographics

The mean age of the study population was 66.0±11.3 years, and male dominance was observed (65%). Perihilar cholangiocarcinoma was the most common location (83.9%), followed by distal bile duct cholangiocarcinoma (13.9%) and diffuse cholangiocarcinoma (2.1%). CEA was not elevated with an average value of 4.5±6.8 ng/ml (reference range: 0-5 ng/ml), but CA-19-9 was elevated to 2,265.9±5,548.7 U/ml (reference range: 0-37 U/ml). The average value of bilirubin was 12.6±9.7 mg/dl. Biliary drainage was performed in 250 patients (89.3%), which included 198 percutaneous transhepatic biliary drainage (PTBD) (70.7%), 29 endoscopic retrograde biliary drainage (ERBD) (10.4%) and 23 endoscopic naso-biliary drainage (ENBD) (8.2%). Only 46 patients (17.1%) were confirmed to have received adjuvant therapy. These demographics are described in Table 1.

Pathologically, there were 5 patients (1.8%) of T1, 29

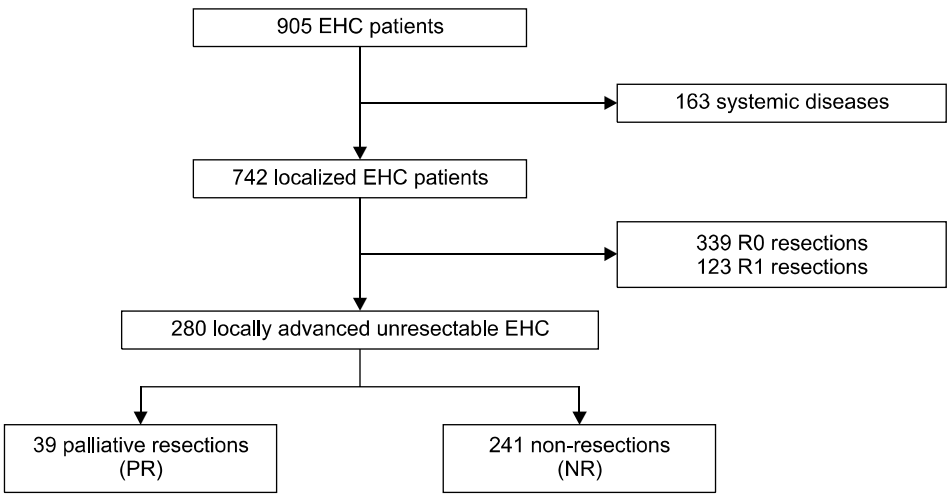


Fig. 1. A summary of selection of patients eligible for analysis is depicted.

Table 1. The clinicopathologic features of locally advanced non-resectable extrahepatic cholangiocarcinoma

Characteristics	Non-resection (N=241)	Palliative resection (R2) (N=39)	Total (N=280)	*p*-value
Age (yrs)	66.1±0.7	65.5±1.7	66.0±0.7	0.751
Gender (M : F)	1.9 : 1 (158 : 83)	1.6 : 1 (24 : 15)	1.9 : 1 (182 : 98)	0.625
Location				0.900
Perihilar	202 (83.8%)	33 (84.6%)	235 (83.9%)	
Distal/Diffuse	39 (16.2%)	6 (15.4%)	45 (16.1%)	
Initial CEA (ng/ml)	4.7±0.6	3.5±0.6	4.5±0.5	0.414
Initial CA 19-9 (U/ml)	2,345.6±510.8	1,959.1±732.6	2,265.9±432.0	0.719
Maximal bilirubin (mg/dl)	12.9±0.7	10.9±1.4	12.6±0.6	0.228
Biliary drainage				0.385
PTBD	168 (69.7%)	30 (76.9%)	198 (70.7%)	
ERBD	27 (11.2%)	2 (5.1%)	29 (10.4%)	
ENBD	18 (7.5%)	5 (12.8%)	23 (8.2%)	
T classification				<0.001
T1	0 (0%)	5 (12.8%)	5 (1.8%)	
T2	17 (7.1%)	12 (30.8%)	29 (10.4%)	
T3	151 (62.7%)	14 (35.9%)	165 (58.9%)	
T4	73 (30.3%)	8 (20.5%)	81 (28.9%)	
N classification.				0.889
N0	76 (31.5%)	19 (48.7%)	95 (33.9%)	
N1	53 (22.0%)	14 (35.9%)	67 (23.9%)	
Nx	*112 (46.5%)*	*6 (15.4%)*	*118 (42.1%)*	*0.001*
Adjuvant therapy	26 (10.8%)	23 (59.0%)	49 (17.5%)	<0.001
Chemotherapy	23 (9.5%)	20 (51.3%)	43 (15.4%)	<0.001
Radiotherapy	13 (5.4%)	22 (56.4%)	35 (12.5%)	<0.001
Follow-up (median, mos)	11.3 (0-57)	29.1 (0-102)	13.8 (0-102)	<0.001

PTBD, percutaneous transhepatic biliary drainage; ERBD, endoscopic retrograde biliary drainage; ENBD, endoscopic naso-biliary drainage

(10.4%) of T2, 165 (58.9%) of T3, and 81 (28.9%) of T4. In terms of lymph node (LN) metastasis, 95 patients (33.9%) had positive LN and 67 had negative LN. The overall median survival of the study population was 10±1 months and the 3- and 5-year survival rates (YSR) were 8.5% and 2.5%, respectively.

Clinicopathologic comparison of PR and NR groups

The mean ages (65.5 vs. 66.1 years, p=0.751) and the gender ratios (1.6 : 1 vs. 1.9 : 1, p=0.625) were not different between NR and PR groups. The tumor location did not differ (83.8% perihilar in NR vs. 84.6% perihilar in PR, p=0.900). The initial CEA (3.5 vs. 4.7 ng/ml, p=0.414), initial CA-19-9 (1,959.1 vs. 2,345.6 U/ml, p=0.719), and highest bilirubin levels (10.9 vs. 12.9 mg/dl, p=0.228) did not reveal any statistical difference between the groups. The biliary drainage method did not differ between NR and PR groups (p=0.385). Although N classification seemed to differ statistically (p=0.001), when comparing N0 and N1 only, the N classification was not different between the groups (p=0.889). These clinicopathologic features are described in Table 2.

The proportions that received adjuvant therapy ($p<0.001$) were significantly different. In terms of adjuvant therapy, only 10.8% of the NR group was confirmed to have received adjuvant therapy whereas 56.4% of the PR group was confirmed. T classification showed a significant difference between the groups. The NR group tended to have higher T classifications ($p<0.001$) with 93.0% of T3/T4 tumors, whereas the PR group had 56.4% of T3/T4 tumors.

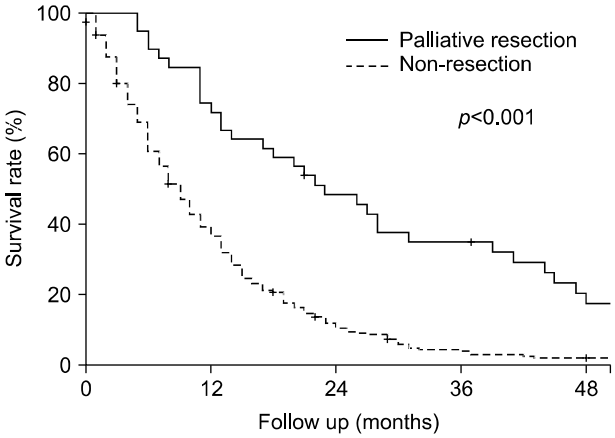
Comparison of survival outcome between PR and NR groups

The median survival, 3-, and 5-YSR of PR group were 23 months, 32.1%, and 13.1%, respectively. For NR group, they were 9 months, 3.9%, and 0%. The survival outcome of PR was significantly better than that of NR ($p<0.001$, Fig. 2).

Table 2. Survival outcome according to various clinicopathologic features

Variable		Case number	Median (Mos)	3-year survival rate (%)	*p*-value
Age	<60/≥60	65/215	9/11	8.7/7.9	0.784
Sex	Male/Female	182/98	10/11	8.7/6.7	0.955
T classification*	T1/T2/T3/T4	5/29/165/81	45/17/9/9	60.0/21.7/6.5/1.4	<0.001
N classification*	N0/N1/Nx	95/67/118	14/8/8	20.5/1.7/2.7	<0.001
Location	Perihilar/Distal/Diffuse	235/39/6	10/8/22	9.3/0/1.7	0.006
Resection	No/Yes	241/39	9/23	3.9/32.1	<0.001
Adjuvant treatment	No/Yes	231/49	9/17	5.2/22.3	<0.001
Chemotherapy	No/Yes	237/43	9/18	5.3/24.4	<0.001
Radiotherapy	No/Yes	245/35	9/23	5.9/23.8	<0.001

*AJCC 6th edition



Status	Median survival	3-YSR	5-YSR
NR (n=241)	9 months	3.9%	0%
PR (n=39)	23 months	32.1%	13.1%

Fig. 2. The survival outcome of palliative resection (PR) was significantly better than that of non-resection (NR).

Survival outcomes according to different clinicopathologic features were assessed. The survival differences were insignificant according to age and gender. On the other hand, survival outcome was different according to T classification, N classification, tumor location, and adjuvant treatment as summarized in Table 3.

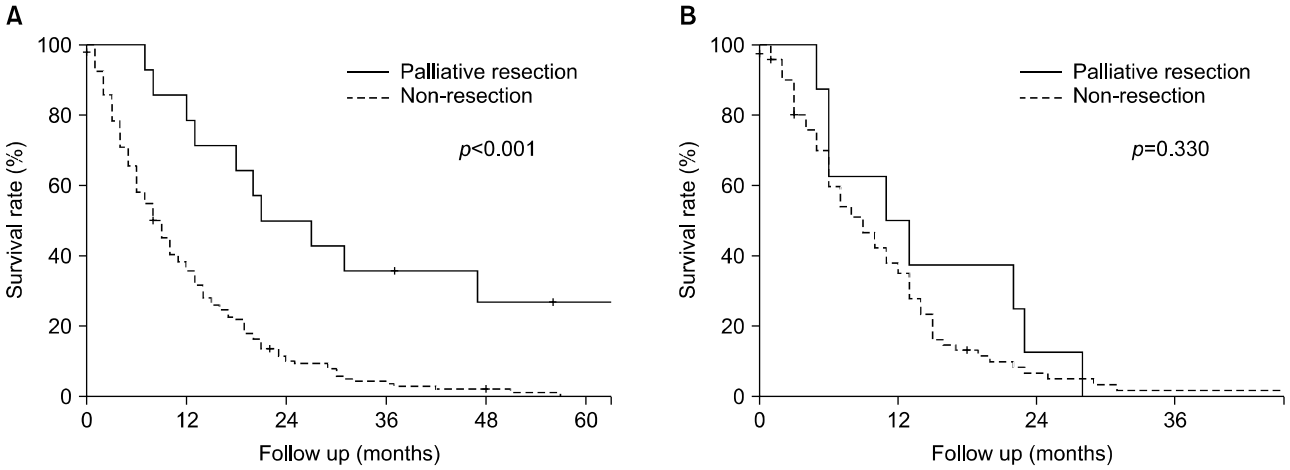
Subgroup analysis of T classification demonstrated that PR showed better survival outcome compared to NR up to T3 with statistical significance (median survival 21 months for PR vs. 9 months for NR, $p<0.001$, Fig. 3A). However, in T4 tumors, the benefit of palliative resection was lost (median survival 11 months for PR vs. 9 months for NR, $p=0.330$, Fig. 3B).

In terms of adjuvant treatment, 49 patients were confirmed to have received adjuvant treatment. These patients received chemotherapy alone, radiation therapy alone, or concurrent chemoradiation therapy. As shown in Fig. 4A, there was a significant difference in survival outcome between patients who received adjuvant treatment. The median survival of those with adjuvant treatment was 17 months whereas the median survival of those without adjuvant treatment was 9 months ($p<0.001$). Both chemotherapy and radiation therapy showed significant survival benefits ($p<0.001$).

Table 3. Multivariate analysis on factors affecting survival outcome

	Relative risk	95% CI	*p*-value
Regional lymph node metastasis	2.084	1.491-2.914	<0.001
Non-resection	2.270	1.497-3.443	<0.001
No chemotherapy	1.604	1.095-2.349	0.015

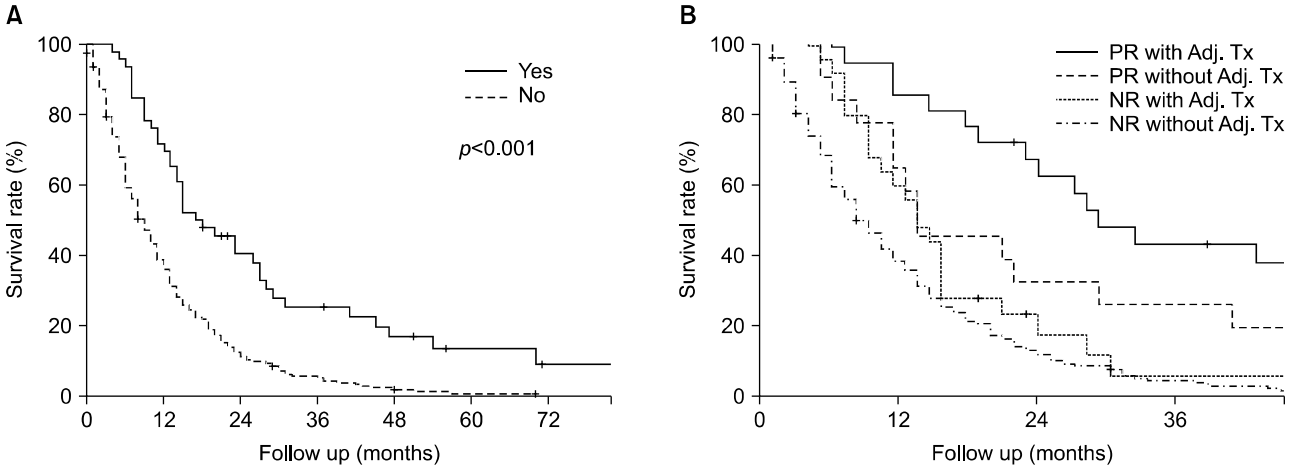
To further evaluate the effect of adjuvant treatment, survival outcome depending on adjuvant therapy in each of PR group and NR group was analyzed. PR with adjuvant treatment showed marginally better survival than PR without adjuvant treatment ($p=0.058$) and significantly better survival than NR groups regardless of adjuvant treatment ($p<0.001$). The survival outcome of PR without adjuvant treatment was second to PR with adjuvant treatment with a median survival of 13 months. Although this was better than NR with adjuvant treatment in terms of 3- and 5-YSR (20.5% and 6.3% for PR without adjuvant treatment vs. 5.6% and 0% for NR with adjuvant treatment), statistical significance was not achieved ($p=0.342$). NR without adjuvant treatment had the worst outcome with median survival of 8 months. This had a marginal difference from NR with adjuvant treatment ($p=0.082$),



Status	Median survival	3-YSR	5-YSR
NR (n=151)	9 months	3.6%	0%
PR (n=14)	21 months	35.7%	26.8%

Status	Median survival	3-YSR	5-YSR
NR (n=73)	9 months	1.6%	0%
PR (n=8)	11 months	0%	0%

Fig. 3. Comparison of survival outcomes in T3 shows that palliative resection have survival benefit (A). However, this survival benefit of palliative resection is no longer valid in T4 tumors (B).



Adjuvant treatment	Median survival	3-YSR	5-YSR
Yes (n=49)	17 months	22.3%	11.0%
No (n=231)	9 months	5.2%	0.6%

	Median (months)	3-YSR (%)	5-YSR (%)	*p*-value (A)	(B)	(C)	(D)
PR+adjuvant treatment (A) (n=23)	28	39.1	21.2		0.058	<0.001	<0.001
PR-adjuvant treatment (B) (n=16)	13	20.5	6.3	0.058	-	0.342	0.006
NR+adjuvant treatment (C) (n=26)	13	5.6	0	<0.001	0.342	-	0.082
NR-adjuvant treatment (D) (n=215)	8	3.7	0	<0.001	0.006	0.082	-

Fig. 4. Adjuvant treatment shows significantly improved survival in locally advanced unresectable EHCs (A). Subgroup survival analysis demonstrates that palliative resection is essential to improve the benefit of adjuvant treatment (Adj. Tx) (B).

and a significant difference from PR without adjuvant treatment (p=0.006). These results are summarized in Fig. 4B.

In order to find independent predictive risk factors, Cox regression multivariate analysis was done with factors that were significant on univariate analysis. Regional LN metastasis (RR, 2.084; 95% CI, 1.491-2.914; $p<0.001$), non-resections (RR, 2.270; 95% CI, 1.497-3.443; $p<0.001$) and no chemotherapy (RR, 1.604; 95% CI, 1.095-2.349; p=0.015) were identified as risk factors for poor outcome (Table 3).

DISCUSSION

Surgical resection of tumor is the only potential therapeutic method and provides long term biliary patency for patients with EHCs and is thus the mainstay of treatment for EHC.[4,11] However, not all EHCs are resectable. There are many factors to be considered in determining the resectability of EHC. The major determinants of resectability include extent of vascular invasion, hepatic lobar atrophy, amount of hepatic parenchyma involved, and extent of spread within the biliary tree. Hepatic lobar atrophy with contralateral portal vein or hepatic artery encasement or contralateral tumor extension to secondary biliary branches may preclude resection. Encasement or occlusion of main portal vein or vessels supplying hepatic remnants are considered contraindications to surgery.[12] The reported resectability rates of EHCs range from 24% to 36%,[9,10,13,14] meaning that about 60% of patients are found in unresectable state. Although there are many reports documenting the outcome of curative resections,[9,10,15-20] little has been studied regarding the outcome of unresectable patients.

The current study focused on non-systemic locally advanced non-resectable EHC. In contrast to the 5-YSRs of R0 resection and R1 resection, which are known to be 30-45% and 14-30%,[4-6,11] the investigated 5-YSR of locally advanced unresectable EHC was 2.5%. Even though this subset of patients has such dismal prognosis, they should not be abandoned and care must be given to achieve longer survival. According to the current result, palliative resection yielded significantly better survival outcome over non-resection and interventional biliary drainage. The median survival for the PR group was 23 months in contrast to 9 months for the NR group. This may imply a potential beneficial role of palliative resection, though it may only be an R2 resection.

An interesting finding is that this survival benefit of palliative resection could no longer be observed in T4 tumors. This may suggest that palliative resection is beneficial to certain point, but once tumor extends beyond that point and becomes far advanced, even palliative resection loses its beneficial role. Therefore, the extent of tumor should be thoroughly explored intraoperatively and should be carefully evaluated for the role of palliative resection.

Among factors that demonstrate a significant difference in survival outcome, adjuvant therapy-along with palliative resection-is another factor in which physicians can intervene. With adjuvant therapy, the median survival was significantly improved from 9 months to 17 months in the current study. However, the effectiveness of chemotherapy and/or radiotherapy is still controversial and inconclusive. Takada et al.[21] conducted a large phase III trial evaluating adjuvant chemotherapy in patients with resected pancreaticobiliary malignancies in 2002. In 139 cholangiocarcinomas, 5-fluorouracil-based adjuvant chemotherapy did not significantly improve 5-YSR in either the curative or non-curative resection patients. Since then, new chemotherapeutic agents have been introduced and various dosages and regimens have been investigated. However, the role of adjuvant chemotherapy in EHC requires further investigation. Furthermore, few studies on the role of adjuvant chemotherapy in locally advanced unresectable tumors have been reported, and this is another area that also needs further investigation. In addition, the role of adjuvant radiotherapy needs to be investigated. Adjuvant radiotherapy is usually reported to have limited survival benefit in EHCs,[22] but there are increasing reports of a potential benefit, especially in positive margin patients.[23-27] Yet, the benefit of radiotherapy in locally advanced unresectable tumor needs to be further elucidated.

According to the current results, although adjuvant treatment seems to provide a survival benefit, adjuvant treatment alone is not sufficient. The survival outcome of PR without adjuvant treatment was similar to or better than that of NR with adjuvant treatment. Furthermore, adjuvant treatment without resection only provided a marginal survival benefit.

Based on our findings, an algorithm may be proposed

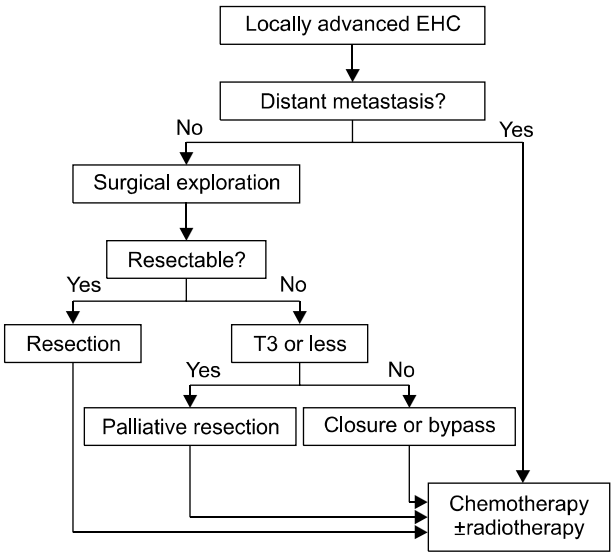


Fig. 5. Management algorithm for locally advanced EHC is depicted.

for locally advanced unresectable EHCs. An EHC patient without evidence of systemic disease should undergo surgical exploration. Even if the tumor is found to be unresectable, the extent of tumor should be evaluated. Should the extent of tumor be equal or less than T3, palliative resection should be performed. However, should the extent of tumor be compatible with T4, resection is no longer necessary and only bypass operation should be done as necessary. Adjuvant treatment should be done. This algorithm is summarized in Fig. 5.

This study has several limitations. First of all, the retrospective nature of this review compromises accuracy and the level of evidence. Second, the small size of the PR group gives inadequate power for statistical significance. Third, because the patients are at advanced stage, some patients give up on further treatment or receive further treatment at a local hospital. This causes many follow-up losses and inaccurate data on adjuvant treatment. Nevertheless, this study was able to demonstrate a potential benefit of palliative resection and adjuvant treatment in locally advanced EHC, warranting further investigation into these issues.

In conclusion, without evidence of systemic disease, palliative resection may provide some survival benefit in selected locally advanced unresectable EHCs. Adjuvant treatment may further improve survival outcome. Further well-designed studies are needed to verify the results of the current study.

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